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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Jordan et al.	)	
Application No.: 09/021,421	)	Group No.: 1614
Filed: February 10, 1998	)	Examiner: Goldberg, J.
For: CHELATED 8-HYDROXYQUINOLINE AND USE THEREOF IN A METHOD OF TREATING EPITHELIAL LESIONS	)	

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents and Trademarks, Washington, DC 20231, on December 26, 2000

Dan Cleveland, Jr.

ASSISTANT COMMISSIONER FOR
PATENTS
WASHINGTON, D.C. 20231

Sir:

DECLARATION OF FRANK S. POTESTIO UNDER RULE 1.132

1. I am Dr. Frank Potestio, M.D., and I am named as an inventor in the above-identified patent application. I am also president of Dermex Pharmaceuticals, which is the assignee of the application. A copy of my curriculum vitae is attached to the Declaration as Exhibit A.

2. This Declaration is submitted for the purpose of providing evidence of unexpectedly enhanced utility in the claimed invention, as well as the criticality of the claimed five percent concentrations of 8-hydroxyquinoline and an escharotic chelatable metal agent. These results have been obtained by numerous researchers who are engaged in research efforts that were organized

under my supervision at Dermex Pharmaceutical. The results that I am reporting herein are based upon information that the researchers have reported to me in my managerial capacity, as well as in many instances my own personal observations.

3. I have reviewed the amended claims in this application, which are attached as Exhibit B. Claim 1 recites that the 8-hydroxyquinoline is present in an amount of at least five percent by weight of the composition, as is the zinc chloride. Based upon human and animal clinical studies that have been reported to me, I believe that these concentrations are critical thresholds for realizing therapeutic benefits from the administration of these compositions, especially in topical applications, though also in injectable and oral forms.

4. The written word is only partially effective in describing the utility of the claimed invention. Pictures are required to present the full story, and this Declaration provides numerous pictures showing a level of *in vivo* efficacy such as I have never encountered in a medical career spanning almost six decades.

5. Exhibit C is a series of five photographs taken from the wrist of an eighty five year old man.

5.1. The first photograph C1 shows an untreated basal cell carcinoma lesion on the right wrist. Surgical excision of this lesion would not likely have been successful in eradicating the carcinoma, and there would likely have been scarring together with restricted motion as a result of surgery.

5.2. The lesion was treated according to the claimed invention. A zinc-chelated solution of 8-hydroxyquinoline was prepared to include a 1:2 ratio of 8-hydroxyquinoline to $ZnCl_2$ (w/w) suspended in glycerine to provide a ten percent weight of 8-hydroxyquinoline in solution. The surface of the lesion was abraded, and the solution was applied topically.

5.3. The second photograph C2 shows the basal cell lesion as necrotic tissue one week after the topical solution was applied without further treatment.

5.4. The third photograph C3 shows removal of the necrotic tissue by forceps. The wound margin was biopsied and the solution was thereafter applied to the wound margin. A pathology report based upon the biopsy confirmed that the wound margin was free from basal cell carcinoma.

5.5. The fourth photograph C4 shows healing of the wound site approximately two weeks after the necrotic tissue was removed.

5.6. The fifth photograph C5 shows complete healing of the wound site including regenerated hair follicles approximately three months after the necrotic tissue was removed.

5.7. A control study was performed using another basal cell lesion on this same patient. The carrier base excluding the 8-hydroxyquinoline and the zinc was applied to this other lesion with no apparent effect for several weeks.

5.8. The patient was monitored for one year, and it was determined that there was no recurrence of the lesion shown in photograph C1.

6. Exhibit D is a series of six photographs showing the treatment of a basal cell carcinoma lesion on the left cheek of a woman aged approximately 85 years.

6.1. The first photograph D1 shows the untreated lesion. Surgical excision of this lesion would not likely have been successful in eradicating the basal cell carcinoma and would have left the patient with a severe disfigurement of the face together with significant facial paralysis.

6.2. The lesion was treated according to the claimed invention. A zinc-chelated solution of 8-hydroxyquinoline was prepared to include a 1:2 ratio of 8-hydroxyquinoline to $ZnCl_2$ (w/w) suspended in glycerine to provide a ten percent weight of 8-hydroxyquinoline in solution. The surface of the lesion was abraded, and the solution was applied topically.

6.3. The second photograph D2 shows the basal cell lesion as necrotic tissue three days after the topical solution was applied.

6.4. The third photograph D3 shows the basal cell lesion as necrotic tissue one week after the topical solution was applied.

6.5. The fourth photograph D4 shows the wound margin underlying the necrotic tissue after the necrotic tissue was removed by forceps. The wound margin was biopsied and the solution was thereafter

applied to the wound margin. A pathology report based upon the biopsy confirmed that the wound margin was free from basal cell carcinoma.

6.6. The fifth photograph D5 shows the wound margin one day after the necrotic tissue was removed.

6.7. The sixth photograph D6 shows complete closure of the wound site approximately three months later with minimal scarring together with regeneration of hair follicles.

6.8. A control study was performed using another basal cell lesion on this same patient. The carrier base excluding the 8-hydroxyquinoline and the zinc was applied to this other lesion with no apparent effect over several weeks.

6.9. The patient was monitored for one year, and it was determined that there was no recurrence of the lesion.

7. Exhibit E is a series of three photographs showing the treatment of a basal cell carcinoma lesion behind the left cheek of a woman aged approximately 69 years.

7.1. The first photograph E1 shows the untreated lesion, which has recurred after an unsuccessful attempt at surgical excision.

7.2. The lesion was treated according to the claimed invention. A zinc-chelated solution of 8-hydroxyquinoline was prepared to include a 1:2 ratio of 8-hydroxyquinoline to $ZnCl_2$ (w/w) suspended in glycerine to provide a ten percent weight of 8-hydroxyquinoline in

solution. The surface of the lesion was abraded, and the solution was applied topically.

7.3. The second photograph E2 shows the wound site of the basal cell lesion after the necrotic tissue was removed by forceps one week after the topical solution was applied. The wound margin was biopsied and the solution was thereafter applied to the wound margin. A pathology report based upon the biopsy confirmed that the wound margin was free from basal cell carcinoma.

7.5. The third photograph E3 shows complete closure of the wound site approximately three months later with minimal scarring together with regeneration of hair follicles.

7.6. A control study was performed using another basal cell lesion on this same patient. The carrier base excluding the 8-hydroxyquinoline and the zinc was applied to this other lesion with no apparent effect over several weeks.

7.7. The patient was monitored for one year, and it was determined that there was no recurrence of the lesion.

9. Exhibit F is a series of four photographs showing the treatment of a basal cell carcinoma lesion on the face and nose of a woman aged approximately 40 years.

9.1. The first photograph F1 shows the untreated lesion. Surgical excision of this lesion would not likely have been successful in eradicating the basal cell carcinoma and would have left the patient

with a severe disfigurement of the face together with some paralysis.

9.2. The lesion was treated according to the claimed invention. A zinc-chelated solution of 8-hydroxyquinoline was prepared in the manner shown in Example 1 of the application. The surface of the lesion was abraded, and the solution was applied topically.

9.3. The second photograph F2 shows the wound site located in place of the former basal cell lesion after forceps removal of necrotic tissue one week after the topical solution was applied. The wound margin was biopsied and the solution was thereafter applied to the wound margin. A pathology report based upon the biopsy confirmed that the wound margin was free from basal cell carcinoma.

9.4. The third photograph F3 shows the wound margin one day after the necrotic tissue was removed.

9.5. The fourth photograph F4 shows complete closure of the wound site approximately three months later with minimal or no scarring together with regeneration of hair follicles.

9.6. The patient was monitored for one year, and it was determined that there was no recurrence of the lesion.

10. Exhibit G is a series of six photographs showing the treatment of a squamous cell carcinoma lesion on the neck of a man aged approximately 60 years.

10.1. The first photograph G1shows the untreated lesion. Surgical excision of this lesion would not likely have been successful in eradicating the basal cell carcinoma and would have left the patient with scarring. Surgery would also have carried significant risk of severing major blood vessels in this area.

10.2. The lesion was treated according to the claimed invention. A zinc-chelated solution of 8-hydroxyquinoline was prepared in the manner shown in Example 1 of the application. The surface of the lesion was abraded, and the solution was applied topically.

10.3. The second photograph G2 shows the wound margin underlying the resultant necrotic tissue after the necrotic tissue was removed by forceps. The wound margin was biopsied and the solution was thereafter applied to the wound margin. A pathology report based upon the biopsy confirmed that the wound margin was free from basal cell carcinoma.

10.4. The third photograph shows the wound margin four days after the necrotic tissue was removed.

10.5. The fourth and fifth photographs G4 and G5 show continuing closure of the wound site at one week and one month after the necrotic tissue was removed.

10.6. The sixth photograph G6 shows complete closure of the wound site approximately three months later with minimal scarring together with regeneration of hair follicles.

10.7. The patient was monitored for one year, and it was determined that there was no recurrence of the lesion.

11. Exhibit H is a series of nine photographs showing the treatment of a fibrosarcoma lesion on the left mouth of a Yorkie terrier.

11.1. The first photograph H1 shows the untreated lesion, which would have justified euthanasia of the dog.

11.2. The lesion was treated according to the claimed invention. An injectable zinc-chelated solution of 8-hydroxyquinoline was prepared in the manner shown in Example 4 of the application. The lesion was injected with approximately five cc's of the solution.

11.3. The second, third and fourth photographs H2-H4 show necrosis of the tumor three days after the injection occurred.

11.4. The fifth, sixth and seventh photographs H5-H7 show continuing necrosis of the tumor through one week after the injection occurred.

11.5. The eighth photograph H8 shows the dog under anesthisia after veterinary surgical removal of deep necrotic tissue, which was debrided from the wound site.

11.6. The ninth photograph H9 shows closure of the wound site one week after surgery to remove the necrotic tissue.

12. Exhibit I is a series of six photographs showing the treatment of anaplastic sarcoma in a domestic cat. Veterinarians have no known cure for this condition, apart from the modalities that are disclosed in the present application, because the lesions recur after surgical excision.

12.1. The first photograph I1 shows the untreated lesion.

12.2. The lesion was treated according to the claimed invention. A zinc-chelated solution of 8-hydroxyquinoline was prepared in the manner shown in Example 1 of the application. The surface of the lesion was shaved, abraded, and the solution was applied topically.

12.3. The second and third photographs I2 and I3 show the lesion as necrotic tissue three days after the topical solution was applied, and the topical solution was then reapplied.

12.4. The fourth photograph I4 shows the lesion as necrotic tissue one week after the topical solution was applied.

12.5. The fifth and sixth photographs I5 and I6 show the cat one week after the necrotic tissue was removed by forceps.

12.6 The cat was euthanized at the request of its owners due to the nature of the wound and the perception that the cat could be in pain. Even so, the composition again demonstrated selectivity and specificity in attacking only the diseased tissue of the lesion.

13. We have produced a large amount of other documentary evidence including cow eye cancer studies, Kaposi sarcoma studies, and equine sarcoid studies. Regardless of the lesion type, whether the lesion is cancerous, precancerous, or a virally induced lesion such as a wart, our invariable experience has been to obtain the same effect that is shown in the preceding exhibits. The claimed composition induces selective necrosis of the diseased tissue.

14. The claimed composition has been used with effect on a Kodiak Bear With Soft Tissue Fibrosarcoma.

14.1. An eight year old male Kodiak bear was diagnosed with a tumor in the dorsolateral region proximate the right carpus. The bear was anaesthetized and the tumor was biopsied. Clinical diagnosis was that of myxoid fibrosarcoma with chondroid differentiation Grade 2. There was a low to medium chance of metastasis. The tumor measured 54.5 cm at the circumference, 17 cm proximal to distal, and 21 cm lateral to base of the tumor. A diagnostic clinician noted some bone invasion and recommended amputation of the afflicted limb.

14.2. Study of the biopsy samples showed a moderately differentiated tumor with different lines of differentiation varying from fibrous tissue to early cartilage type tissue. Cells included spindle cells forming bundles that intersected at various angles. Myxomatous and fibrous stroma were present. Nuclei were mildly pleomorphic, oval, and had prominent nucleoli. Mitoses were occasionally present, and there were occasional giant nuclear forms. In some areas, the cells were fibrous. In other areas, the cells were plump with myxoid material or early embryonic cartilagenous type material. One area showed an anaplasia where the cells also had some giant nuclear forms and increased mitotic rates. There were no normal tissue margins.

14.3. An injectable solution was prepared by mixing a quantity of ten percent zinc 8-hydroxyquinoline in a 1:2 molar ratio of 8-hydroxyquinoline to zinc chloride to in isopropyl alcohol. 5 cc were injected into the center of the tumor mass, and 3cc were injected into each of four fingers of the tumor. The tumor was surgically removed two weeks later. Biopsy confirmed that the remaining tumor was encapsulated at the time it was removed, and that the tumor had shrunk 50% in mass. No bone invasion was seen at the time that the tumor was surgically removed.

15. Mammals, including human and veterinary patients, have been treated for a variety of lesions, which are recited in claim 1. The claimed composition selectively attacks lesion and leaves the healthy tissue intact.

16. The claimed composition has additionally been used to cure a variety of other conditions including scabies and bites of the brown recluse spider.

17. At least two veterinarians have reported to me instances in which a solution of twenty percent 8-hydroxyquinoline and forty percent zinc chloride solution has been topically applied to an externally visible tumor in a dog, and the solution has selectively dissolved the tumor through several inches of tissue until bone was visible underneath.

18. Human patients often complain of an intense burning sensation when compositions including about ten percent by weight 8-hydroxyquinoline and twenty percent zinc chloride are applied topically. This sensation is due largely

to the escharotic activity of the zinc chloride. This concentration may be increased up to forty percent of the solution weight without escharotic sloughing of tissue in cases where the lower concentrations require repeat dosages. In the case of Exhibit I, it is doubtful that the cat would have been euthanized pursuant to the owners' request if repeat treatments had not been required and the duration of treatment had not extended too long.

19. On the other hand, the intense burning sensation can be mitigated by reduced dosages of zinc chloride and 8-hydroxyquinoline in combination, which may require repeat applications as applied to various lesions. For example, a full strength solution used to treat papilloma virus located on the male or female reproductive organs is therapeutically effective but causes almost unendurable pain. The solution may be reduced in strength to avoid the high level of discomfort, but repeat applications may be required. Thus, there is a tradeoff that physicians may argue about, namely, whether it is better to implement my preference of a single more intensely painful session that is almost certain to eradicate the lesion, or to have a series of less painful sessions with some uncertainty in the outcome.

20. Our studies have shown that, while concentrations of 8-hydroxyquinoline and zinc chloride may be reduced for the reasons discussed above, there is a threshold at about the five percent concentration level in which the therapeutic effects diminish. Solutions having less than about ten percent 8-hydroxyquinoline and twenty percent zinc chloride may require repeat applications, while solutions having less than five percent of 8-hydroxyquinoline

and five percent zinc chloride most often lack therapeutic effect in topical application in the sense that they are unable to eradicate the lesion.

21. I do not mean to say that reduced concentrations of zinc chloride and 8-hydroxyquinoline are completely without therapeutic effects. The reduced concentration compositions may be useful, for example, as oral maintenance dosages for patients having cancer that is in remission. On the other hand, I do mean to say that our studies have shown reduced concentrations have diminishing utility in the eradication of existing lesions until the lesions become difficult or impossible to control at the threshold level of about five percent.

22. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 12-20-00 By: Frank S. Potestio MD

Frank S. Potestio, M.D.